REMARKS

I. Status Summary

Claims 1, 6, and 8 are pending in the present U.S. patent application and have been examined by the United States Patent and Trademark Office (hereinafter "the Patent Office").

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Cereijido *et al.* (1993) Suppl 17 *J Cell Science* 127-132 (hereinafter "Cereijido") in view of Grunicke *et al.* (1996) 36 *Advan Enzyme Regul* 385-407 (hereinafter "Grunicke").

Claims 9-27 have been canceled without prejudice. Applicants hereby respectfully reserve the right to file one or more divisional applications with claims directed to the subject matter of the claims canceled herein.

Reconsideration of the application based on the application as amended and in light of the remarks set forth below is respectfully requested.

II. Response to the Obviousness Rejection

Claims 1, 6, and 8 have been rejected under 35 U.S.C. § 103(a), upon the contention that the claims are unpatentable over Cereijido in view of Grunicke. According to the Patent Office, Cereijido teaches that inhibition of phospholipase C reduces the development of the transepithelial electrical resistance (TER; also abbreviated as TEER), which the Patent Office asserts is a measure for the paracellular transport through cells, and activation of phospholipase C increases TER. Thus, the Patent Office contends that one of ordinary skill in the art would understand *a priori* that phospholipase C plays an important role in paracellular transport across the intestinal epithelium and that upon administration of a phospholipase C inhibitor the paracellular membrane permeability would be enhanced (*see* Official Action at page 4).

The Patent Office further asserts that Grunicke teaches that hexadecylphosphocholine (HePC, Miltefosine, n = 15) is an inhibitor of PI-specific phospholipase C, and further that it was well known in the art at the time of the invention that HePC was identified as a prototype of the alkylphosphocholines, and that among the phosphocholines, HePC emerged as one of the most active compounds in the

series for the treatment of experimental tumors (*citing* Grunicke at page 386). From this, the Patent Office asserts that one of ordinary skill in the art, upon a search for a phospholipase C inhibitor in the form of an alkylphosphocholine, would have easily recognized the potential of Miltefosine and its close analogues as a phospholipase C inhibitor to enhance paracellular permeability given the teaching of Cereijido in view of Grunicke.

After careful consideration of the rejection and the Patent Office's basis therefor, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully submit that the Patent Office has misinterpreted the teaching of Cereijido, which suggests that inhibition of phospholipase C reduces and its activation increases the development TEER, in concluding that this would teach one of ordinary skill in the art that inhibition of phospholipase C would cause an increase in paracellular permeability across established tight junctions. The evidence presented in Cereijido showing that the TRH (an activator of phospholipase C) increases, and neomycin (an inhibitor of phospholipase C) blocks the development of, TEER is based on a Ca^{2+}-switch experiment that can only test the effect of TRH and neomycin on the formation of tight junctions that have been disrupted by removal of Ca^{2+} from the extracellular medium. This is set forth in the discussion in Cereijido starting from the last paragraph of column 2 on page 129 through the end of second paragraph of column 1 on page 131, including Figures 4 and 5. In fact, the legend to Figure 5 describes the role of phospholipase C in the incorporation of tight junction proteins into the membrane (*i.e.*, the formation of the tight junction) by stimulating their phosphorylation.

Thus, applicants respectfully submit that the experiments disclosed in Cereijido, which relate to the formation of tight junctions, do not teach anything about modulation of the permeability of tight junctions that have already formed and that are present in differentiated enterocytes. In fact, applicants respectfully submit that to the best of their knowledge, no evidence exists that shows that either TRH or neomycin modulates the permeability of pre-formed tight junctions.

Additionally, applicants respectfully submit that Cereijido provides neither direct evidence nor any other source to substantiate the claim that TRH is an activator of

phospholipase C. Similarly, no evidence or citation is provided by Cereijido that neomycin is an inhibitor of phospholipase C. Applicants respectfully contend that TRH has numerous effects, and so does neomycin. Therefore, even if these agents activate and inhibit phospholipase C activity, one of ordinary skill cannot conclude that their effect on the "development" of TEER is via their effect on phospholipase C activity. Taken together, applicants respectfully submit that Cereijido provides at best speculation regarding the role of phospholipase C in the formation of tight junctions, and thus at best offers an invitation to experiment. This invitation to experiment also fails to provide a reasonable expectation for success, and thus does not support a rejection under 35 U.S.C. § 103.

Therefore, applicants respectfully submit that the disclosure of Cereijido does not provide any motivation for one of ordinary skill in the art to look at alkylphosphocholines (APCs) generally as modulators of PLC for the purpose of modulating paracellular permeability in enterocytes that have already completed formation of tight junctions.

Turning now to the disclosure of Grunicke, applicants respectfully submit that Grunicke does not cure this deficiency. The Patent Office asserts that Grunicke teaches that hexadecylphosphocholine (HePC) is an inhibitor of PI-specific phospholipase C. The Patent Office further contends that it was well known in the art at the time of the invention that HePC was a prototype of the alkylphosphocholines, and that among the phosphocholines, HePC emerged as one of the most active compounds in the series for the treatment of tumors.

Applicants respectfully submit that according to Grunicke, HePC inhibited PKC as well as phospholipase D, in addition to inhibiting PI-specific phoshpolipase C, in the NIH 3T3 cells employed. Applicants further respectfully submit that Grunicke did not identify HePC as a prototype of alkylphosphocholines. Rather, they identified HePC as a member of a group of phospholipid analogs, none of which contained alkyl chains connected to a phosphocholine group (*see e.g.*, Figure 1). Instead, these analogs contained serine groups, cyclic analogs of choline, arsenic-containing analogs of choline, or a phosphono group (*e.g.*, replacing a phosphate ester). Therefore, applicants respectfully submit that contrary to the Patent Office's assertion, Grunicke does not support the instant rejection.

Accordingly, applicants respectfully submit that the Patent Office's assertion that Cereijido would have provided a motivation for one of ordinary skill in the art to "search for a phospholipase C inhibitor in the form of an alkylphosphocholine" (*see* Official Action at page 4) in order to modulate paracellular permeability is based on an inaccurate interpretation of this reference. Applicants further respectfully submit that when Cereijido is interpreted in its proper context, no motivation can be found to searching for PLC inhibitors for the purpose of modulating paracellular permeability, and thus one of ordinary skill in the art would not have been motivated to turn to Grunicke at all.

Therefore, applicants respectfully submit that the Patent Office's combination of Cereijido and Grunicke is based on improper hindsight reasoning in that it requires that the teachings of the instant specification with respect to PLC inhibition and paracellular permeability provide the motivation to combine the references. Applicants respectfully submit that without the inclusion of the information provided in the instant specification, it was not known that PLC inhibitors generally, and APCs specifically, had this activity.

As such, applicants respectfully submit that the combination of Cereijido and Grunicke does not support a rejection of claims 1, 6, and 8 under 35 U.S.C. § 103(a). Applicants therefore respectfully request that the instant rejection of claims 1, 6, and 8 be withdrawn at this time, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

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DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge the amount of $60.00 for the Extension of Time fee and any other fees associated with the filing of this Response E, and to credit any over payment, to Deposit Account Number **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

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